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# Bayesian Model Discrimination for Glucose-Insulin Homeostasis

*Cobal 2*

*February 2005*

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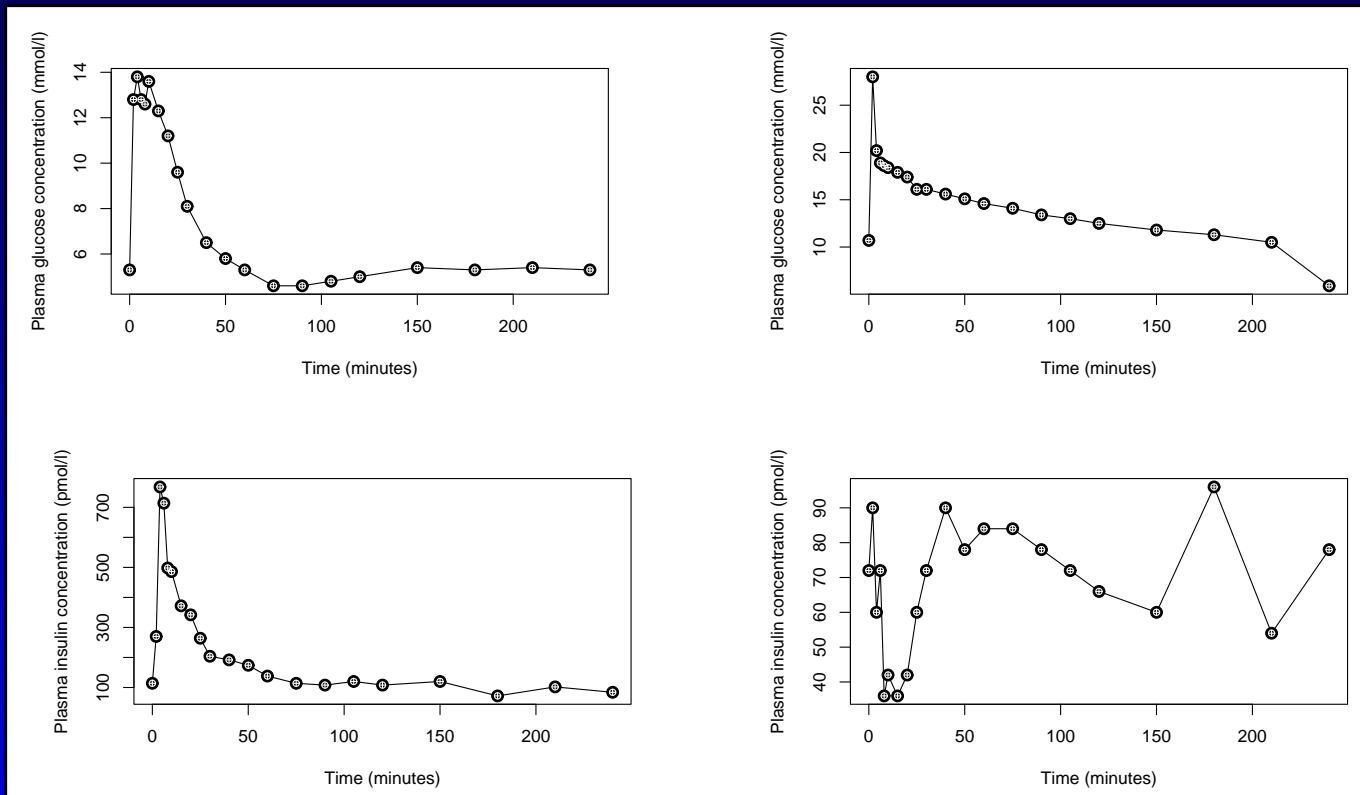
\*\*Statistical Laboratory, University of Cambridge, UK

# Data

## IVGTT: Intra-Venous Glucose Tolerance Test

Sampling of **glucose** and **insulin** concentrations in plasma following an **intravenous glucose injection**.

### Healthy

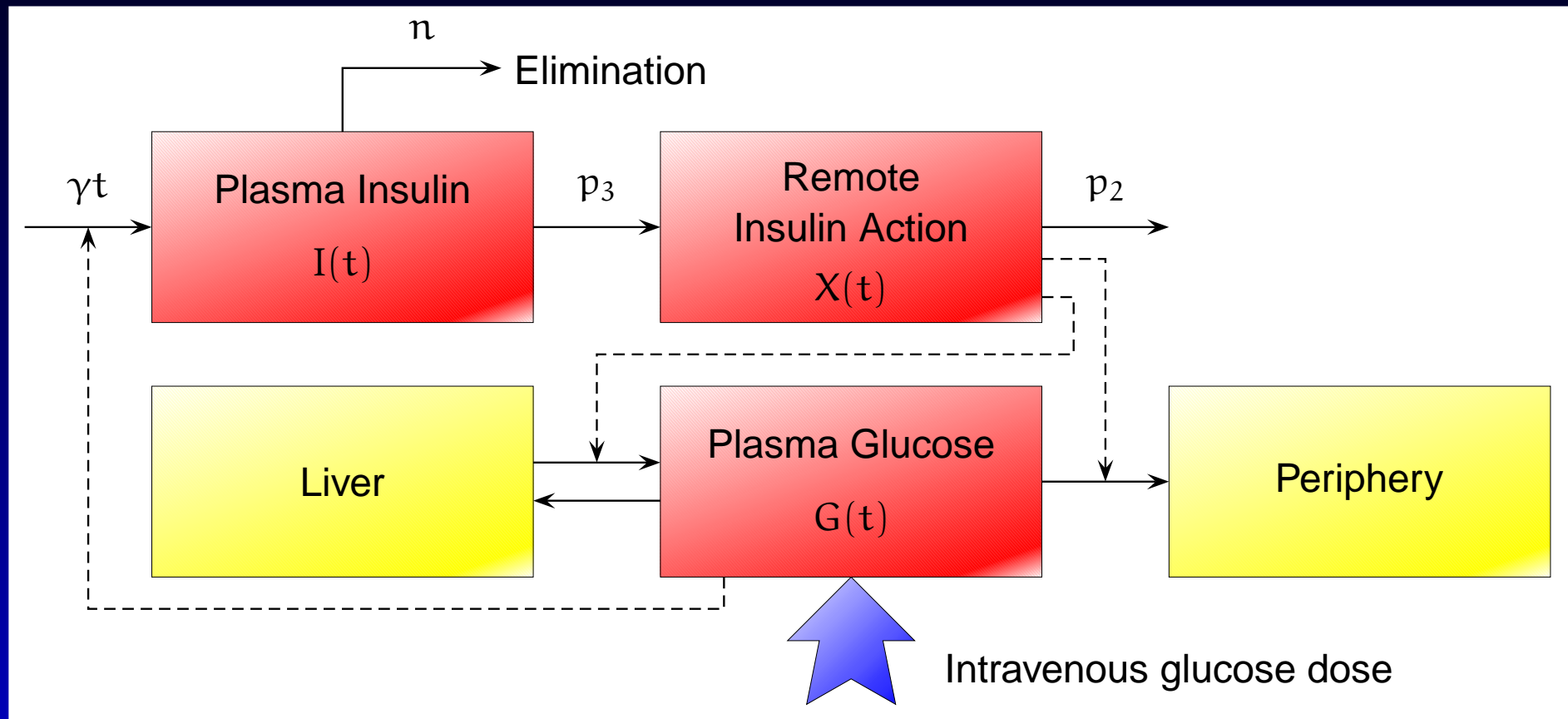


### Type II diabetic

Data on the human body's response to increased blood sugar levels.

# Models – The Minimal Model

**The Minimal Model:** Bergman et al (1979) and Toffolo et al (1980)



$$G_1: \quad \dot{G}(t) = -p_1(G(t) - G_b) - X(t)G(t) \quad G(0) = G_0$$

$$\dot{X}(t) = -p_2X(t) + p_3(I(t) - I_b) \quad X(0) = 0$$

$$I_2: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma J_+(G(t) - h)t \quad I(0) = I_0$$

# Models – The Minimal Model

## Parameters of Interest in the Minimal Model:

insulin sensitivity:	$S_I = p_3/p_2$
glucose effectiveness:	$S_G = p_1$
pancreatic responsiveness:	$\varphi_1 = (I_0 - I_b)/[n(G_0 - G_b)]$ $\varphi_2 = \gamma \times 10^4$

## Current Approach:

Iterative nonlinear least squares technique (MINMOD PROGRAMME)

- not a unified system (the insulin is treated as known).
- $S_I$  estimated close to zero with negative confidence intervals.
- $\varphi_1$  and  $\varphi_2$  not estimated (the insulin is treated as known).
- the positive truncation  $J$  is physiologically questionable.
- the multiplicative effect of time  $t$  is difficult to justify biologically.
- no account of individual variability or process error.

Alternative models and/or other approaches are called for.

# Models – Variations on the Minimal Model

## Variations on the Minimal Model:

Three additional variants of the insulin component:

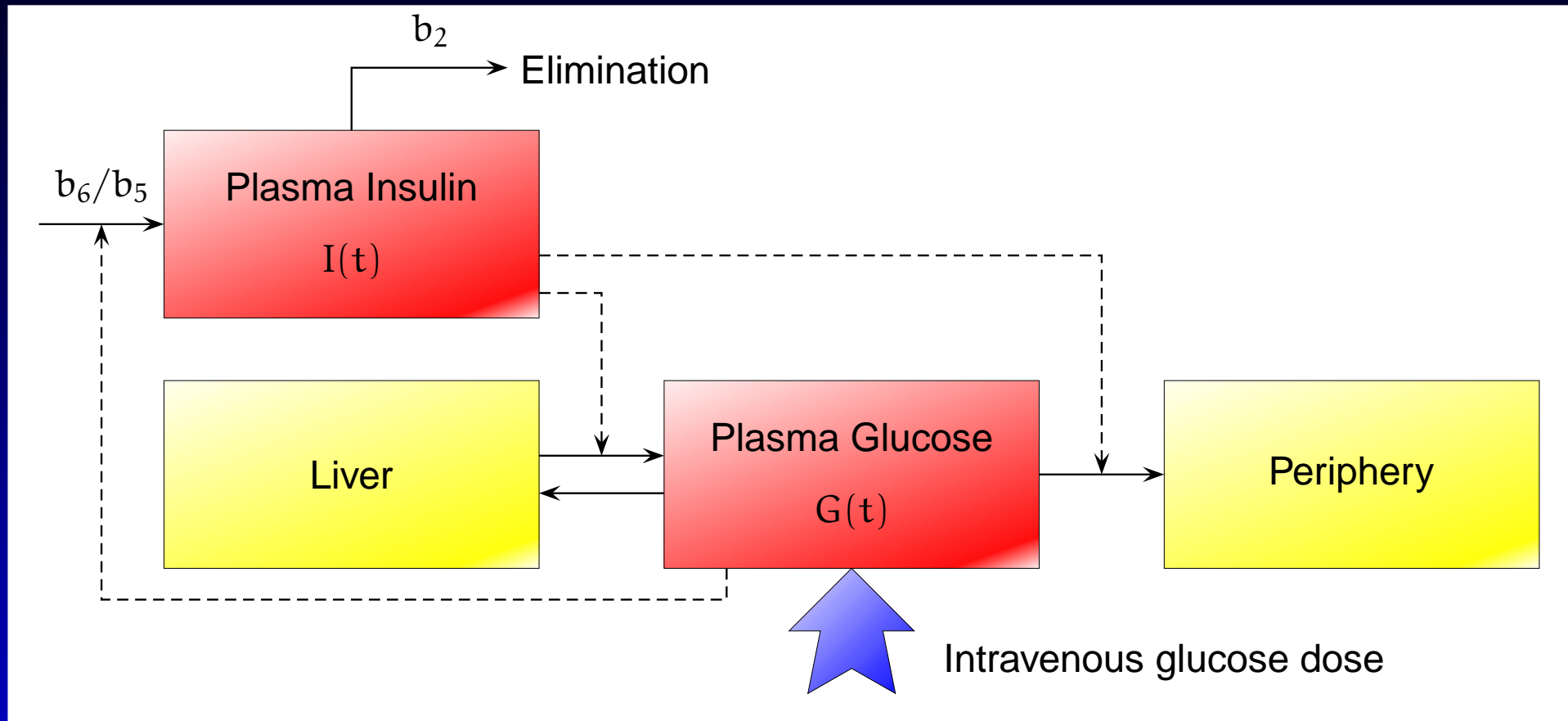
$$I_2: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma J_+(G(t) - h) \quad I(0) = I_0$$

$$I_3: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h)t \quad I(0) = I_0$$

$$I_4: \quad \dot{I}(t) = -n(I(t) - I_b) + \gamma(G(t) - h) \quad I(0) = I_0$$

# Models – The de Gaetano & Arino Model

The GA Model: De Gaetano & Arino (2000)



$$G_2: \quad \dot{G}(t) = -b_1 G(t) - b_4 I(t)G(t) + b_7 \quad G(0) = G_b + b_0$$

$$I_5: \quad \dot{I}(t) = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^t G(s) ds \quad I(0) = I_b + b_3 b_0$$

where  $G(t) \equiv G_b$  for  $t \in [-b_5, 0)$ .

# Models – The de Gaetano & Arino Model

## Parameters of interest:

insulin sensitivity:	$S_I = b_4$
glucose effectiveness:	$S_G = b_1$
pancreatic responsiveness:	$\varphi_1 = b_3/b_2$
	$\varphi_2$ not estimated under the GA model

## Reformulating the models

Same approach as Andersen & Højbjerg (2005):

- The glucose and insulin concentrations are **log-transformed** (same scale - common variance).
- The DE's are **discretised**.
- Impose **random errors** both on the system and the measurements.
- Extend to **population** modelling.



A stochastic **state space modelling** framework that allows for **likelihood constructions**.



**You may flip this page if you dare**

# Reformulating the Models

## Log-Transformation:

$$\begin{aligned} g(t) &= \log G(t), & x(t) &= \log X(t) & \text{and } i(t) &= \log I(t) \\ \dot{g}(t) &= \dot{G}(t)/G(t), & \dot{x}(t) &= \dot{X}(t)/X(t) & \text{and } \dot{i}(t) &= \dot{I}(t)/I(t) \end{aligned}$$

Reparameterizing by  $S_I$ ,  $S_G$ ,  $\varphi_1$ ,  $\varphi_2$ ,  $b_0$  and  $b_3$ .

## Log-Transformed Minimal Model:

$$\begin{aligned} G_1: \dot{g}(t) &= -S_G(1 - G_b e^{-g(t)}) - e^{x(t)} & g(0) &= \log(G_b + b_0) \\ \dot{x}(t) &= -p_2(1 - S_I(e^{i(t)} - I_b)e^{-x(t)}) & x(0) &\rightarrow -\infty \\ I_1: \dot{i}(t) &= -\frac{b_3}{\varphi_1}(1 - e^{-i(t)}I_b) + 10^{-4}e^{-i(t)}\varphi_2 J_+(e^{g(t)} - h)t & i(0) &= \log(I_b + b_3 b_0) \end{aligned}$$

## Discretised Log-transformed Minimal Model

$\Lambda = \{t_1, t_2, \dots, t_{|\Lambda|}\}$  and new notation:  $g(t_k) = g_{t_k}^s$ ,  $x(t_k) = x_{t_k}^s$  and  $i(t_k) = i_{t_k}^s$

$$g_{t_k}^s = g_{t_{k-1}}^s - (t_k - t_{k-1})(S_G(1 - G_b e^{-g_{t_{k-1}}^s}) + e^{x_{t_{k-1}}^s}) + \epsilon^{g^s}$$

$$x_{t_k}^s = x_{t_{k-1}}^s - (t_k - t_{k-1})p_2(1 - S_I(e^{i_{t_{k-1}}^s} - I_b)e^{-x_{t_{k-1}}^s}) + \epsilon^{x^s}$$

$$i_{t_k}^s = i_{t_{k-1}}^s - (t_k - t_{k-1})\left(\frac{b_3}{\varphi_1}(1 - e^{-i_{t_{k-1}}^s}I_b) - 10^{-4}e^{-i_{t_{k-1}}^s}\varphi_2 J_+(e^{g_{t_{k-1}}^s} - h)t_{k-1}\right) + \epsilon^{i^s}$$

where  $\epsilon^{g^s}$ ,  $\epsilon^{x^s}$  and  $\epsilon^{i^s}$  follows  $\mathcal{N}(0, \nu^{-1}(t_k - t_{k-1}))$ .

# Reformulating the Models

## System processes:

$$g_{t_k}^s | g_{t_{k-1}}^s, x_{t_{k-1}}^s, \nu \sim \mathcal{N}(f_{t_{k-1}}^g, \nu^{-1}(t_k - t_{k-1}))$$

$$x_{t_k}^s | x_{t_{k-1}}^s, i_{t_{k-1}}^s, \nu \sim \mathcal{N}(f_{t_{k-1}}^x, \nu^{-1}(t_k - t_{k-1})), \quad t_k \in \Lambda$$

$$i_{t_k}^s | i_{t_{k-1}}^s, g_{t_{k-1}}^s, \nu \sim \mathcal{N}(f_{t_{k-1}}^i, \nu^{-1}(t_k - t_{k-1}))$$

where

$$f_{t_{k-1}}^g = g_{t_{k-1}} - (t_k - t_{k-1}) (S_G (1 - G_b e^{-g_{t_{k-1}}}) + e^{x_{t_{k-1}}})$$

$$f_{t_{k-1}}^x = x_{t_{k-1}} - (t_k - t_{k-1}) p_2 (1 - S_I (e^{i_{t_{k-1}}} - I_b) e^{-x_{t_{k-1}}})$$

$$f_{t_{k-1}}^i = i_{t_{k-1}} - (t_k - t_{k-1}) \left( \frac{b_3}{\varphi_1} (1 - e^{-i_{t_{k-1}}} I_b) - 10^{-4} e^{-i_{t_{k-1}}} \varphi_2 J_+(e^{g_{t_{k-1}}} - h) t_{k-1} \right)$$

## Observed processes:

$$g_{t_k}^o | g_{t_k}^s, \nu_{g^o}^{-1} \sim \mathcal{N}(g_{t_k}^s, \nu_{g^o})$$

$$i_{t_k}^o | i_{t_k}^s, \nu_{i^o}^{-1} \sim \mathcal{N}(i_{t_k}^s, \nu_{i^o}), \quad t_k \in \mathcal{T} \subseteq \Lambda$$

The other models can be reformulated similarly.

# Population Modelling

System processes for individual  $j$  in model  $m$ :

$$\Phi_{jm}^s = \begin{cases} \{g_{jmt_k}^s, x_{jmt_k}^s, i_{jmt_k}^s\}_{t_k \in \Lambda} & \text{for } m = 1, \dots, 5, \quad (G_1 \times I_1, \dots, I_5) \\ \{g_{jmt_k}^s, i_{jmt_k}^s\}_{t_k \in \Lambda} & \text{for } m = 6, \dots, 10, \quad (G_2 \times I_1, \dots, I_5) \end{cases}$$

Observed processes for individual  $j$ :

$$\Phi_j^o = \{g_{jt_k}^o, i_{jt_k}^o\}_{t_k \in \mathcal{T}}$$

Distributional assumptions for individual  $j$  in model  $m$ :

$$p_m(\Phi_{jm}^s | \theta_{jm}) \propto \begin{cases} \nu_j^{|\Lambda|} \exp(-V_m(\Phi_{jm}^s, \theta_{jm})) & \text{for } m = 1, \dots, 5 \\ \nu_j^{3|\Lambda|/2} \exp(-V_m(\Phi_{jm}^s, \theta_{jm})) & \text{for } m = 6, \dots, 10 \end{cases}$$

$$p_m(\Phi_j^o | \theta_{jm}, \Phi_{jm}^s) \propto (\nu_{g_j^o} \nu_{i_j^o})^{|\mathcal{T}|/2} \exp(-W(\Phi_j^o, \Phi_{jm}^s, \theta_{jm}))$$

where

$$\theta_{jm} = \begin{cases} (S_{Gj}, S_{Ij}, \varphi_{1j}, b_{3j}, b_{0j}, G_{bj}, I_{bj}, \varphi_{2j}, p_{2j}, h_j, \nu_j, \nu_{g_j^o}, \nu_{i_j^o}) & \text{for } m = \{1, \dots, 9\} \setminus 5 \\ (S_{Gj}, S_{Ij}, \varphi_{1j}, b_{3j}, b_{0j}, G_{bj}, I_{bj}, b_{5j}, \nu_j, \nu_{g_j^o}, \nu_{i_j^o}) & \text{for } m = 5 \text{ and } 10 \end{cases}$$

# Population Modelling – cont'd

and

$$V_m(\Phi_{jm}^s, \theta_{jm}) = \begin{cases} \frac{1}{2} \nu_j \sum_{t_k \in \Lambda} (g_{jmt_k}^s - f_{jmt_k}^g)^2 + (x_{jmt_k}^s - f_{jmt_k}^x)^2 + (i_{jmt_k}^s - f_{jmt_k}^i)^2 & m=1, \dots, 5 \\ \frac{1}{2} \nu_j \sum_{t_k \in \Lambda} (g_{jmt_k}^s - f_{jmt_k}^g)^2 + (i_{jmt_k}^s - f_{jmt_k}^i)^2 & m=6, \dots, 10 \end{cases}$$

$$W(\Phi_j^o, \Phi_{jm}^s, \theta_{jm}) = \frac{1}{2} \sum_{t_k \in \mathcal{T}} \nu_{g_j^o} (g_{jt_k}^o - g_{jmt_k}^s)^2 + \nu_{i_j^o} (i_{jt_k}^o - i_{jmt_k}^s)^2$$

**Likelihood for population of L individuals in model m:**

$$L(\Psi_m, \theta_m, \Phi_m^s | \Phi^o) = \prod_{j=1}^L p_m(\Phi_j^o | \theta_{jm}, \Phi_{jm}^s) p_m(\Phi_{jm}^s | \theta_{jm}) p_m(\theta_{jm} | \Psi_m)$$

where

$$\Phi_m^s = (\Phi_{1m}^s, \Phi_{2m}^s, \dots, \Phi_{Lm}^s)$$

$$\Phi^o = (\Phi_1^o, \Phi_2^o, \dots, \Phi_L^o)$$

$$\theta_m = (\theta_{1m}, \theta_{2m}, \dots, \theta_{Lm})$$

and  $p_m(\theta_{jm} | \Psi_m)$  is the product of log-normal (for the system parameters) and gamma distributions (for the precisions).

# Bayesian Analysis

## Posterior Distribution: MCMC Methods (Metropolis-Hastings)

$$\pi(\Psi, \theta, \Phi^s | \Phi^o) \propto \prod_{j=1}^L p(\Phi_j^o | \theta_j, \Phi_j^s) p(\Phi_j^s | \theta_j) p(\theta_j | \Psi) p(\Psi)$$

where  $p(\Psi)$  prior for the population parameters - a product of normal (for the means) and gamma (for the precisions) distributions.

## Model Uncertainty: Reversible Jump MCMC

$$\pi(\Psi_m, \theta_m, \Phi_m^s, m | \Phi^o) \propto \prod_{j=1}^L p_m(\Phi_j^o | \theta_{jm}, \Phi_{jm}^s) p_m(\Phi_{jm}^s | \theta_{jm}) p_m(\theta_{jm} | \Psi_m) p(\Psi_m | m) p(m)$$

where  $p(m)$  prior for model index - uniform.

## Improving Mixing: Simulated Tempering (RJ)MCMC

$$\pi_\tau(\Psi_m, \theta_m, \Phi_m^s, m | \Phi^o) \propto \prod_{j=1}^L \left( p_{m,\tau}(\Phi_j^o | \theta_{jm}, \Phi_{jm}^s) p_{m,\tau}(\Phi_{jm}^s | \theta_{jm}) \right)^{s(\tau)} \\ \times p_m(\theta_{jm} | \Psi_m) p(\Psi_m | m) p(\tau | m) p(m)$$

where  $p(\tau | m)$  prior for temperature  $\tau$  (coarseness level of discretisation) and

$s(\tau) = 2^{-(\tau-1)n}$  for  $n > 0$ . Note,  $\tau = 1$  provides the posterior.

# Results

## Posterior Model Probability:

		Posterior model probability									
Population	Coarseness	1	2	3	4	5	6	7	8	9	10
Healthy	1	0.00	0.21	0.76	0.03	0.00	0.00	0.00	0.00	0.00	0.00
	2	0.10	0.15	0.23	0.20	0.08	0.02	0.07	0.08	0.05	0.01
	4	0.11	0.13	0.12	0.10	0.10	0.16	0.07	0.05	0.09	0.06
Diabetic	1	0.00	0.00	0.07	0.00	0.01	0.00	0.00	0.75	0.00	0.17
	2	0.05	0.09	0.15	0.07	0.08	0.04	0.13	0.20	0.08	0.11
	4	0.13	0.05	0.11	0.10	0.07	0.08	0.14	0.13	0.12	0.09

# Results

Simulated values of  $m$  and  $\tau$ :

Healthy population

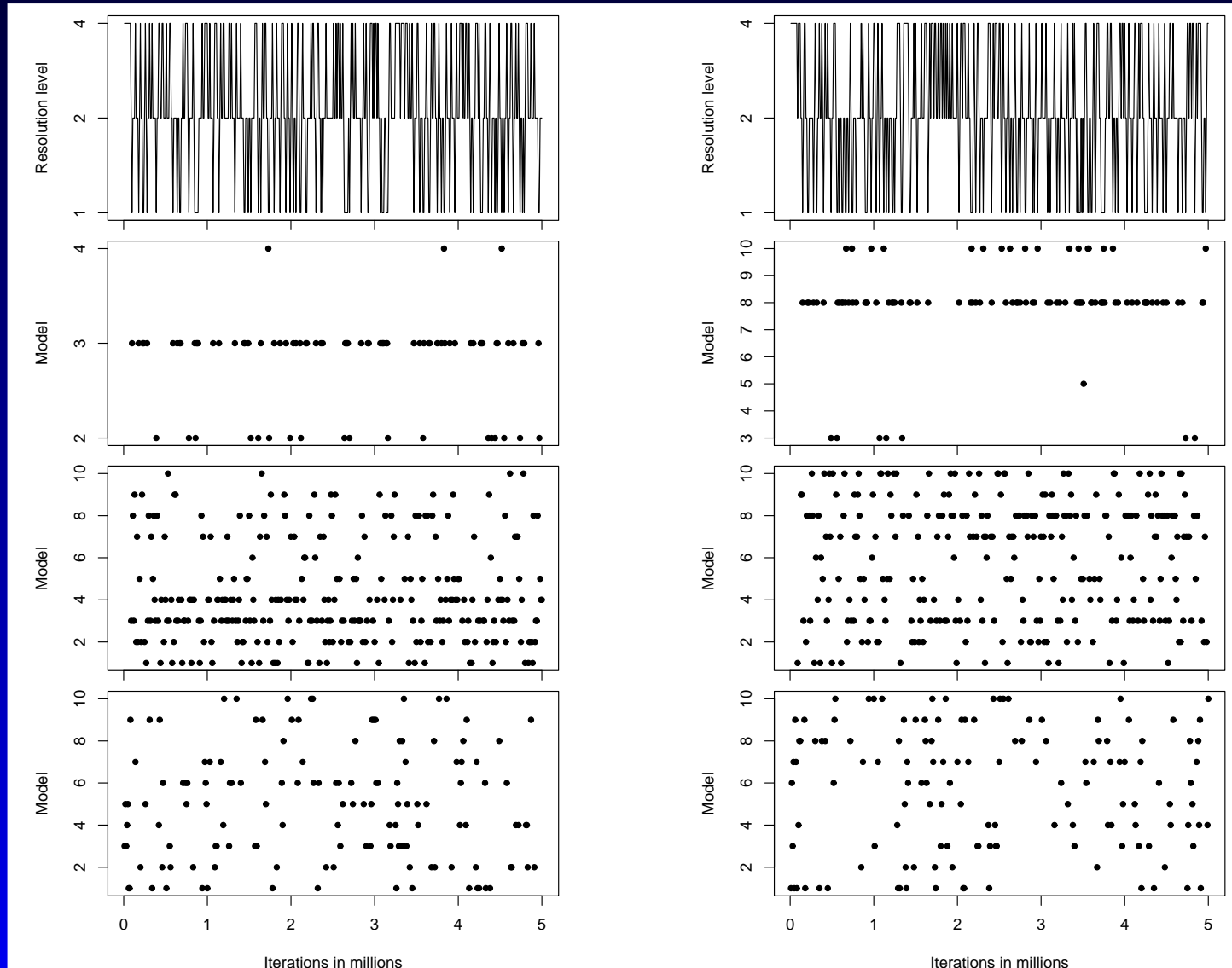
Type II diabetic population

Coarseness

$\tau = 1$

$\tau = 2$

$\tau = 3$



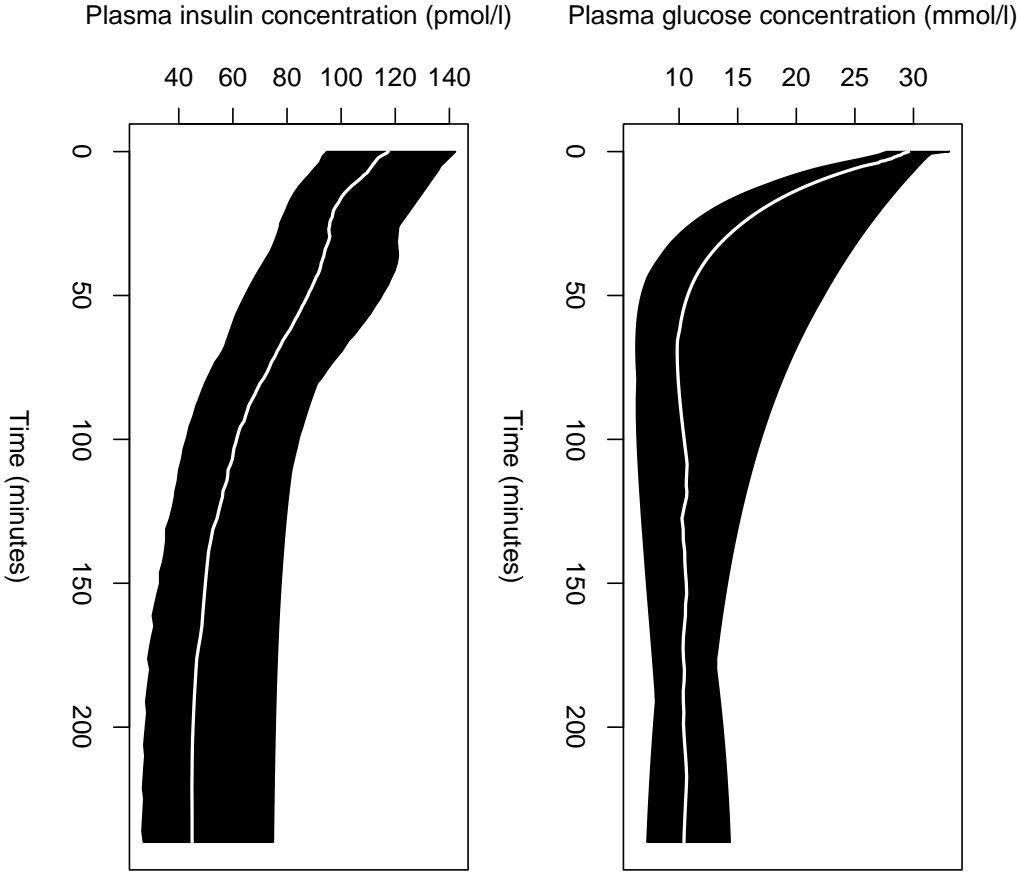
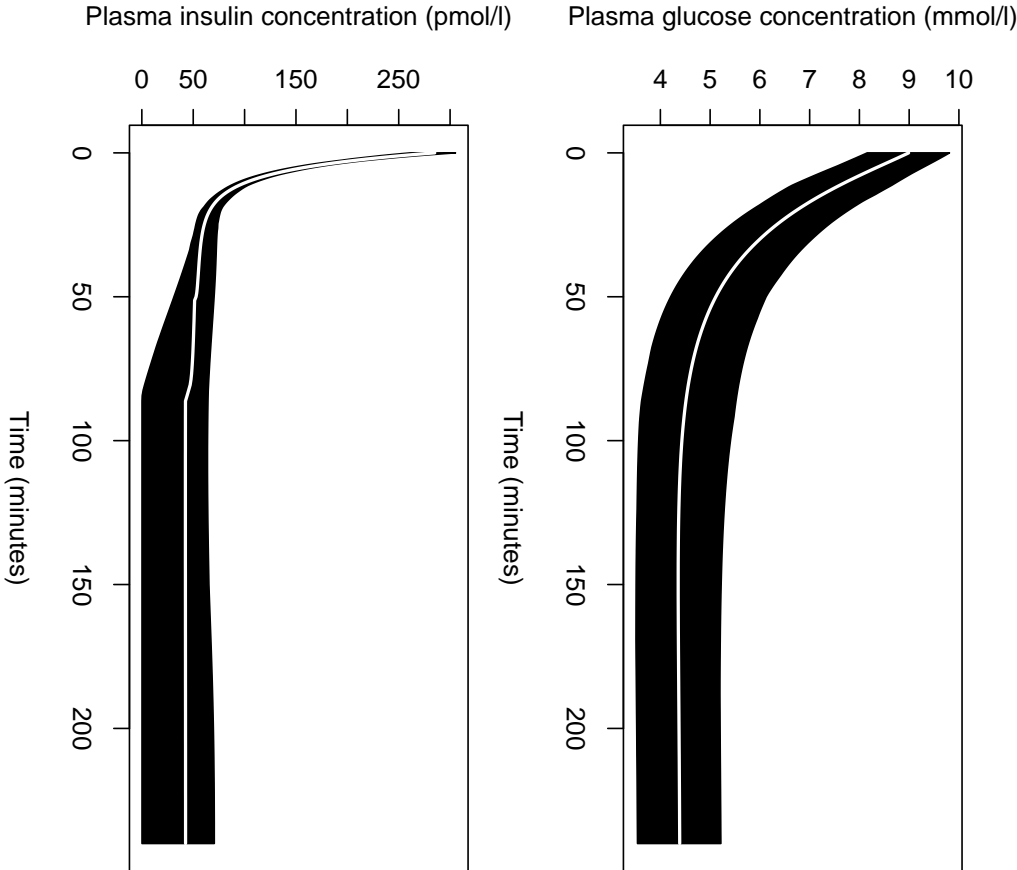


# Results

## Posterior Population Glucose and Insulin Concentrations:

Healthy

Type II diabetic



# Discussion

## Results:

- Discriminating among 10 glucose and insulin models.



Healthy population: Minimal model with no positive relection (original model)

Diabetic population: Original insulin minmal model and new glucose model.

- Providing model-averaged inference on parameters of interest.
- Unified systems of both glucose and insulin.
- No  $S_I = 0$  problems for diabetic population.
- Possible to estimate  $\varphi_1$  and  $\varphi_2$ .
- Random errors on system and measurements.
- Population modelling.

For more details see Andersen, Brooks and Højbjerg(2004) - download from

<http://www.math.aau.dk/research/reports/R-2004-15.pdf>

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